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(54) Intermediates and process for preparing olanzapine

Zwischenprodukte und Verfahren zur Herstellung Olanzapin

Produits intermédiaires et procédé pour la préparation d'olanzapine

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Description

[0001] This invention relates to a process for preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (referred to herein as "olanzapine"), and to certain dihydrate intermediates.

[0002] Olanzapine is useful for treating psychotic patients and is currently being investigated for such use. Applicants have discovered that Form II olanzapine is the most stable anhydrous form of olanzapine, providing a stable anhydrous formulation with pharmaceutically desired characteristics, (See European Patent Specification No. 733,635). Careful preparation and controlled conditions are necessary to assure substantially pure Form II olanzapine product (hereinafter referred to as "Form II"); however, Applicants have discovered a process for preparing the desired Form II using a dihydrate olanzapine intermediate under aqueous conditions. In certain situations, Form II which has been prepared from an aqueous solvent may be particularly advantageous. Such Form II material prepared from an aqueous solvent provides assurance that the Form II material is free of substantially all organic solvent residues. This process can provide an especially ecologically desirable method for providing the desired Form II.

[0003] The presently claimed invention provides dihydrate olanzapine which is especially useful as an intermediate for the preparation of Form II olanzapine. The crystalline form may be particularly advantageous.

[0004] An especially preferred dihydrate is the stable crystalline Dihydrate D olanzapine polymorph (herein referred to as "Dihydrate D") having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (**d**) as set forth in Table 1:

Table 1

d
9.4511
7.7098
7.4482
6.9807
6.5252
5.7076
5.5539
5.223
4.9803
4.8908
4.784
4.6947
4.4271
4.3956
4.3492
4.2834
4.1156
3.7837
3.7118
3.5757
3.482
3.3758
3.3274
3.2413
3.1879
3.135
3.0979
3.016
2.9637
2.907
2.8256
2.7914
2.7317

Table 1 (continued)

d
2.6732
2.5863

[0005] Another especially preferred dihydrate intermediate is the crystalline Dihydrate B olanzapine polymorph (hereinreferred to as "Dihydrate B") having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (**d**) as set forth in Table 2:

Table 2

d
9.9045
6.9985
6.763
6.4079
6.1548
6.0611
5.8933
5.6987
5.4395
5.1983
5.0843
4.9478
4.7941
4.696
4.5272
4.4351
4.3474
4.2657
4.1954
4.0555
3.9903
3.9244
3.8561
3.8137
3.7671
3.6989
3.6527
3.5665
3.4879
3.3911
3.3289
3.2316
3.1982
3.1393
3.0824
2.9899
2.9484
2.9081
2.8551
2.8324
2.751

Table 2 (continued)

d
2.7323
2.6787
2.6424
2.5937

[0006] Another preferred dihydrate intermediate is the crystalline Dihydrate E olanzapine polymorph (herein referred to as "Dihydrate E") having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (**d**) as set forth in Table 3:

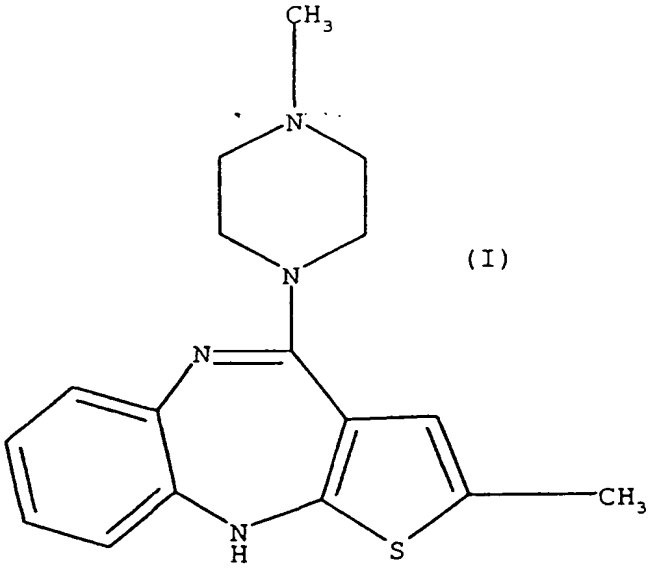
Table 3

d
9.8710
9.5514
6.9575
6.1410
6.0644
5.9896
5.8774
4.7721
4.6673
4.5171
4.4193
4.3540
4.2539
4.2369
4.0537
4.0129
3.8555
3.7974
3.6846
3.5541
3.4844
3.4740
3.4637
3.3771
3.1245
2.9403

[0007] The x-ray powder diffraction patterns set forth herein were obtained with a copper k of wavelength = 1.541 Å. The interplanar spacings in the column marked "d" are reported in Angstroms. The detector was a Kevex silicon lithium solid state detector.

[0008] The presently claimed invention further provides a process for preparing Form II olanzapine comprising drying an olanzapine dihydrate, for instance, in a vacuum oven, at 40°C to 70°C until the desired Form II is formed.

[0009] Applicants have discovered that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, which is a compound of Formula(I):



(I)

exists as two different anhydrous forms which are distinguishable by x-ray powder diffractometry. The most stable anhydrous form has been designated Form II. Though Form II must be prepared using carefully controlled conditions, Applicants have discovered that an olanzapine dihydrate can be used for the preparation of Form II. (see U.S. patent No. 5, 229, 382).

[0010] The polymorph obtainable by the process taught in the '382 patent is an anhydrate form which is not as desirable for pharmaceutical formulations as Form II. The anhydrate obtainable by the process of the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

d
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255
4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817

(continued)

d
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

[0011] A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
6.2439	5.21
5.5895	1.10
5.3055	0.95
4.9815	6.14
4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40
2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10

(continued)

d	I/I_1
2.5956	1.73

[0012] The x-ray powder diffraction patterns herein were obtained with a copper K_a of wavelength I = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

[0013] As used herein "substantially pure" refers to Form II associated with less than 20% solvated and less than 5% Form I, preferably less than 5% solvated and/or Form I, and more preferably less than 1% solvated and Form I. Further, "substantially pure" Form II will contain less than 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual organic solvent.

[0014] Advantageously, the polymorph prepared using the process and intermediates of this invention will be free from chemical solvates, for instance existing as the substantially pure Form II.

[0015] It is especially preferred that the dihydrate intermediate is selected from the group consisting of pure Dihydrate B, Dihydrate D, and Dihydrate E. As used herein the term "pure" refers to less than 20% undesired Dihydrate. More preferredly, the term refers to less than 10% undesired dihydrate. It may be especially preferred that "pure" refers to less than 5% undesired dihydrate.

[0016] A typical example of an x-ray diffraction pattern for Dihydrate D is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.4511	100.00
7.7098	14.23
7.4482	22.43
6.9807	5.73
6.5252	5.45
5.7076	4.24
5.5539	1.60
5.223	62.98
4.9803	22.21
4.8908	15.03
4.784	27.81
4.6947	5.15
4.4271	13.00
4.3956	16.63
4.3492	34.43
4.2834	51.38
4.1156	18.32
3.7837	5.30
3.7118	1.56
3.5757	0.71
3.482	9.39
3.3758	24.87
3.3274	13.49
3.2413	5.97
3.1879	1.04
3.135	3.18
3.0979	1.43
3.016	1.95
2.9637	0.48
2.907	2.42
2.8256	7.46

(continued)

d	I/I_1
2.7914	3.61
2.7317	1.47
2.6732	5.19
2.5863	10.62

[0017] The x-ray powder diffraction patterns herein were obtained with a copper K_a of wavelength 1 = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

[0018] A typical example of an x-ray diffraction pattern for the Dihydrate B polymorph is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.9045	100.00
6.9985	0.39
6.763	0.17
6.4079	0.13
6.1548	0.85
6.0611	0.99
5.8933	0.35
5.6987	0.12
5.4395	1.30
5.1983	0.67
5.0843	0.24
4.9478	0.34
4.7941	6.53
4.696	1.26
4.5272	2.65
4.4351	2.18
4.3474	1.85
4.2657	0.49
4.1954	0.69
4.0555	0.42
3.9903	0.89
3.9244	1.52
3.8561	0.99
3.8137	1.44
3.7671	0.92
3.6989	1.78
3.6527	0.60
3.5665	0.34
3.4879	1.41
3.3911	0.27
3.3289	0.20
3.2316	0.31
3.1982	0.19
3.1393	0.35
3.0824	0.18
2.9899	0.26
2.9484	0.38

(continued)

d	I/I_1
2.9081	0.29
2.8551	0.37
2.8324	0.49
2.751	0.37
2.7323	0.64
2.6787	0.23
2.6424	0.38
2.5937	0.21

[0019] A typical example of an x-ray diffraction pattern for Dihydrate E is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.9178	100.00
9.6046	16.75
7.0163	2.44
6.1987	8.78
6.0971	10.62
5.9179	1.73
4.8087	50.14
4.714	10.24
4.5335	14.20
4.4531	7.80
4.3648	3.04
4.276	4.50
4.0486	2.76
3.8717	5.09
3.8292	13.39
3.7053	17.24
3.5827	4.82
3.4935	13.22
3.3982	2.01
3.3294	1.30
3.2026	0.98
3.145	2.66
3.1225	1.63
3.088	2.11
2.9614	2.49
2.9014	1.03
2.8695	2.06
2.8359	1.63
2.7647	1.95
2.7582	1.68
2.7496	1.84
2.7421	1.03
2.7347	1.36
2.6427	2.01

[0020] The x-ray powder diffraction patterns herein were obtained with a copper K_a of wavelength 1 = 1.541Å. The

interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

[0021] A typical example of an x-ray diffraction pattern for the anhydrous Form II polymorph is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

[0022] As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

[0023] The compounds and processes of the present invention are useful for preparing compounds having beneficial central nervous system activity. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

[0024] Some prefered characteristics of this invention include the following:

A) An intermediate dihydrate which is the Dihydrate D polymorph of olanzapine;
B) A compound which is the substantially pure Dihydrate D polymorph;
C) An intermediate dihydrate which is the Dihydrate B polymorph of olanzapine;
D) An intermediate dihydrate which is the Dihydrate E polymorph of olanzapine;
E) Process for preparing Form II comprising drying an olanzapine dihydrate in a vacuum oven at about 50°C.;
F) Form II prepared using a dihydrate is used for treating a condition selected from the group consisting of a

psychosis, schizophrenia, a schizophreniform disorder, mild anxiety, and acute mania;
G) A formulation comprising Form II and substantially pure Dihydrate D; and
H) A formulation comprising Form II and substantially pure Dihydrate B.

[0025] The starting materials for the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art. The material to be employed as starting materials in the process of this invention can be prepared by the general procedure taught by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety.

[0026] The Dihydrate D is prepared by extensive stirring of technical olanzapine, which may be prepared as described by Preparation 1, under aqueous conditions. The term "aqueous conditions" refers to an aqueous solvent which may be either water or a solvent mixture comprising water and an organic solvent which is sufficiently water miscible to allow the required stoichiometric quantity of water to be present in the solvent mixture. If a solvent mixture is utilized, then the organic solvent must be removed, leaving behind the water, and/or replaced with water. The term "extensive stirring" shall be from about one (1) hour to about six (6) days; however, the artisan will appreciate that the time will vary with the reaction conditions such as temperature, pressure, and solvent. It may be preferred that extensive stirring refers to at least four (4) hours. It is preferred that the aqueous conditions include an aqueous solvent.

[0027] The completion of the reaction may be monitored using x-ray powder diffraction and other such methods familiar to the skilled artisan. Several such techniques are described below.

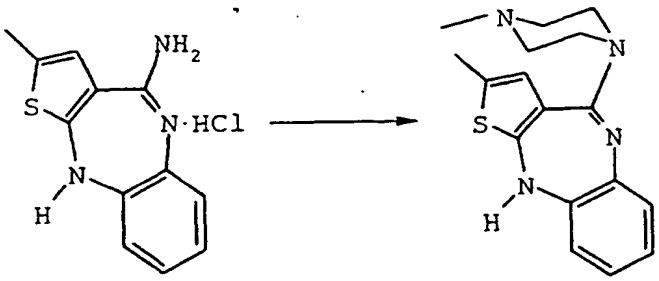
[0028] Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetery (DSC), titrametric analysis for water, and H^1-NMR analysis for solvent content.

[0029] The dihyrates described herein are true dihydrates having two water molecules per drug molecule, wherein the water molecules are incorporated into the crystalline lattice of the dihydrate compound.

[0030] The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

Preparation 1

Technical Grade olanzapine



Intermediate 1

[0031] In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical)	6 volumes
Intermediate 1	75 g
N-Methylpiperazine (reagent)	6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

[0032] A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions

were followed by HPLC until 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine. Yield: 76.7%; Potency: 98.1%

Example 1

Dihydrate D

[0033] A 100 g sample of technical grade olanzapine (see Preparation 1) was suspended in water (500 mL). The mixture was stirred at about 25°C for about 5 days. The product was isolated using vacuum filtration. The product was identified as Dihydrate D olanzapine using x-ray powder analysis. Yield: 100 g. TGA mass loss was 10.2%.

Example 2

Dihydrate E

[0034] A 0.5 g sample of technical grade olanzapine was suspended in ethyl acetate (10 mL) and toluene (0.6 mL). The mixture was heated to 80°C until all the solids dissolved. The solution was cooled to 60°C and water (1 mL) was added slowly. As the solution cooled to room temperature, a crystal slurry formed. The product was isolated using vacuum filtration and dried under ambient conditions. The product was identified as Dihydrate E using x-ray powder analysis and solid state ^{13}C NMR. TGA mass loss was 10.5%. Yield: 0.3 g.

Example 3

Dihydrate B

[0035] A 10 g sample of technical grade olanzapine was suspended in water (88 mL). The mixture was stirred at about 25°C for 6 hours. The product was isolated using vacuum filtration. The product was identified as Dihydrate B olanzapine using x-ray powder analysis. Yield: 10.86 g.

Example 4

Form II

[0036] The Dihydrate D of olanzapine, prepared as described by Example 1, is dried in a vacuum oven at about 50°C under about 100 to 300 mm vacuum for a period of about 27 hours. The resulting material is identified using x-ray powder analysis and identified as Form II.

Example 5

[0037] The Dihydrate B of olanzapine, is dried in a vacuum oven at about 50 °C under about 100 to 300 mm vacuum for a period of about 30 hours. The resulting material is identified using x-ray powder analysis and identified as Form II.

Example 6

[0038] The Dihydrate E of olanzapine, is dried in a vacuum oven at about 50 °C under about 100 to 300 mm vacuum for a period of about 30 hours. The resulting material is identified using x-ray powder analysis and identified as Form II.

Claims

1. A compound which is an olanzapine dihydrate.

2. A compound of **Claim 1** wherein the dihydrate is an intermediate for preparing Form II olanzapine.

3. A compound of **Claim 1** wherein the dihydrate is crystalline Dihydrate B olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (**d**) as set forth in Table 2:

Table 2

d
9.9045
6.9985
6.763
6.4079
6.1548
6.0611
5.8933
5.6987
5.4395
5.1983
5.0843
4.9478
4.7941
4.696
4.5272
4.4351
4.3474
4.2657
4.1954
4.0555
3.9903
3.9244
3.8561
3.8137
3.7671
3.6989
3.6527
3.5665
3.4879
3.3911
3.3289
3.2316
3.1982
3.1393
3.0824
2.9899
2.9484
2.9081
2.8551
2.8324
2.751
2.7323
2.6787
2.6424
2.5937

4. A Dihydrate B of **Claim 3** wherein a typical relative intensity pattern is the following:

d	I/I_1
9.9045	100.00
6.9985	0.39
6.763	0.17
6.4079	0.13
6.1548	0.85
6.0611	0.99
5.8933	0.35
5.6987	0.12
5.4395	1.30
5.1983	0.67
5.0843	0.24
4.9478	0.34
4.7941	6.53
4.696	1.26
4.5272	2.65
4.4351	2.18
4.3474	1.85
4.2657	0.49
4.1954	0.69
4.0555	0.42
3.9903	0.89
3.9244	1.52
3.8561	0.99
3.8137	1.44
3.7671	0.92
3.6989	1.78
3.6527	0.60
3.5665	0.34
3.4879	1.41
3.3911	0.27
3.3289	0.20
3.2316	0.31
3.1982	0.19
3.1393	0.35
3.0824	0.18
2.9899	0.26
2.9484	0.38
2.9081	0.29
2.8551	0.37
2.8324	0.49
2.751	0.37
2.7323	0.64
2.6787	0.23
2.6424	0.38
2.5937	0.21

5. A dihydrate of **Claim 4** wherein the dihydrate is pure, that is, contains less than 20% undesired dihydrate.

6. A compound of **Claim 1** wherein the dihydrate is crystalline Dihydrate E olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (**d**) as set forth in Table 3:

Table 3

d
9.8710
9.5514
6.9575
6.1410
6.0644
5.9896
5.8774
4.7721
4.6673
4.5717
4.4193
4.3540
4.2539
4.2369
4.0537
4.0129
3.8555
3.7974
3.6846
3.5541
3.4844
3.4740
3.4637
3.3771
3.1245
2.9403

7. A Dihydrate E of **Claim 6** wherein a typical relative intensity patern is the following:

d	I/I_1
9.9178	100.00
9.6046	16.75
7.0163	2.44
6.1987	8.78
6.0971	10.62
5.9179	1.73
4.8087	50.14
4.714	10.24
4.5335	14.20
4.4531	7.80
4.3648	3.04
4.276	4.50
4.0486	2.76
3.8717	5.09
3.8292	13.39
3.7053	17.24
3.5827	4.82
3.4935	13.22
3.3982	2.01

(continued)

d	I/I_1
3.3294	1.30
3.2026	0.98
3.145	2.66
3.1225	1.63
3.088	2.11
2.9614	2.49
2.9014	1.03
2.8695	2.06
2.8359	1.63
2.7647	1.95
2.7582	1.68
2.7496	1.84
2.7421	1.03
2.7347	1.36
2.6427	2.01

8. A compound of **Claim 7** wherein the dihydrate is pure, that is, contains less than 20% undesired dihydrate.

9. A process for preparing substantially pure Form II containing less than 0.5% undesired chemical impurities or residual organic solvent, comprising drying an olanzapine dihydrate until the desired Form II is prepared.

10. A process of **Claim 9** wherein the dihydrate is dried in a vacuum oven at 40°C to 70°C.

11. A process of **Claim 10** wherein the dihydrate is Dihydrate D.

12. A process of **Claim 10** wherein the dihydrate is Dihydrate B.

13. A process of **Claim 10** wherein the dihydrate is Dihydrate E.

Patentansprüche

1. Verbindung, bei der es sich um eine Olanzapindihydrat handelt.

2. Verbindung nach Anspruch 1, wobei das Dihydrat ein Zwischenprodukt zur Herstellung der Form II von Olanzapin ist.

3. Verbindung nach Anspruch 1, wobei das Dihydrat ein kristallines Dihydrat-B-Olanzapin-Polymorph mit einem typischen Röntgenpulverbeugungsmuster ist, das sich durch die folgenden Gitterebenenabstände d, die in Tabelle 2 angegeben sind, wiedergeben läßt:

Tabelle 2

d
9.9045
6.9985
6.763
6.4079
6.1548
6.0611
5.8933
5,6987

Tabelle 2 (fortgesetzt)

5.4395
5.1983
5.0843
4.9478
4.7941
4.696
4.5272
4.4351
4.3474
4.2657
4.1954
4.0555
3.9903
3.9244
3.8561
3.8137
3.7671
3.6989
3.6527
3.5665
3.4879
3.3911
3.3289
3.2316
3.1982
3.1393
3.0824
2.9899
2.9484
2.9081
2.8551
2.8324
2.751
2.7323
2.6787
2.6424
2.5937

4. Dihydrat B nach Anspruch 3, wobei das typische relative Intensitätsmuster das folgende ist:

d	I/I_1
9.9045	100.00
6.9985	0.39
6.763	0.17
6.4079	0.13
6.1548	0.85
6.0611	0.99
5.8933	0.35
5.6987	0.12
5.4395	1.30
5.1983	0.67

(fortgesetzt)

5.0843	0.24
4.9478	0.34
4.7941	6.53
4.696	1.26
4.5272	2.65
4,4351	2.18
4.3474	1.85
4.2657	0.49
4.1954	0.69
4.0555	0.42
3.9903	0.89
3.9244	1.52
3.8561	0.99
3.8137	1.44
3.7671	0.92
3.6989	1.78
3.6527	0.60
3.5665	0.34
3.4879	1.41
3.3911	0.27
3.3289	0,20
3.2316	0.31
3.1982	0.19
3.1393	0.35
3.0824	0.18
2.9899	0.26
2.9484	0.38
2.9081	0.29
2.8551	0.37
2.8324	0.49
2.751	0.37
2.7323	0,64
2.6787	0.23
2.6424	0.38
2.5937	0.21

5. Dihyarat nach Anspruch 4, wobei das Dihydrat rein ist, d.h. weniger als 20% unerwünschtes Dihydrat enthält.

6. Verbindung nach Anspruch 1, wobei das Dihydrat ein kristallines Dihydrat-E-Olanzapin-Polymorph mit einem typischen Röntgenpulverbeugungsmuster ist, das sich durch die folgenden Gitterebenenabstände d, die in der Tabelle 3 angegeben sind, wiedergeben läßt;

Tabelle 3

d
9.8710
9.5514
6.9575
6.1410
6.0644
5.9896
5.8774

Tabelle 3 (fortgesetzt)

4.7721
4.6673
4.5171
4.4193
4.3540
4.2539
4.2369
4.0537
4.0129
3.8555
3.7974
3.6846
3.5541
3.4844
3.4740
3.4637
3.3771
3.1245
2.9403

7. Dihydrat E nach Anspruch 6, wobei das typische relative Intensitätsmuster das folgende ist:

d	I/I_1
9,9178	100.00
9.6046	16.75
7,0163	2,44
6.1987	8.78
6,0971	10.62
5,9179	1,73
4.8087	50.14
4,714	10.24
4.5335	14.20
4.4531	7.80
4.3648	3.04
4.276	4.50
4.0486	2.76
3.8717	5.09
3.8292	13.39
3.7053	17.24
3.5827	4.82
3.4935	13.22
3.3982	2.01
3.3294	1.30
3.2026	0.98
3.145	2.66
3.1225	1.63
3.088	2.11
2.9614	2.49
2.9014	1.03
2.8695	2.06
2.8359	1.63

(fortgesetzt)

d	I/I_1
2.7647	1.95
2.7582	1.68
2.7496	1.84
2.7421	1.03
2.7347	1.36
2.6427	2.01

8. Verbindung nach Anspruch 7, wobei das Dihydrat rein ist, d.h. weniger als 20% unerwünschtes Dihydrat enthält,

9. Verfahren zur Herstellung einer im wesentlichen reinen Form II, die weniger als 0,5% unerwünschte chemische Verunreinigungen oder restliches organisches Lösungsmittel enthält, durch Trocknen eines Olanzapindihydrats, bis die gewünschte Form II erhalten wird.

10. Verfahren nach Anspruch 9, wobei das Dihydrat in einem Vakuumofen bei 40°C bis 70°C getrocknet wird.

11. Verfahren nach Anspruch 10, wobei das Dihydrat das Dihydrat D ist.

12. Verfahren nach Anspruch 10, wobei das Dihydrat das Dihydrat B ist.

13. Verfahren nach Anspruch 10, wobei das Dihydrat das Dihydrat E ist.

Revendications

1. Composé qui est un dihydrate d'olanzapine.

2. Composé de la revendication 1, dans lequel le dihydrate est un intermédiaire pour la préparation d'olanzapine de forme II.

3. Composé de la revendication 1, dans lequel le dihydrate est un polymorphe cristallin de dihydrate B d'olanzapine présentant un spectre de diffraction de rayons X réalisé sur la poudre caractéristique comme représenté par les espaces (d) suivants entre les plans comme présenté dans le tableau 2

Tableau 2

d
9,9045
6,9985
6,763
6,4079
6,1548
6,0611
5,8933
5,6987
5,4395
5,1983
5,0843
4,9478
4,7941
4,696
4,5272
4,4351
4,3474

Tableau 2 (suite)

d
4,2657
4,1954
4,0555
3,9903
3,9244
3,8561
3,8137
3,7671
3,6989
3,6527
3,5665
3,4879
3,3911
3,3289
3,2316
3,1982
3,1393
3,0824
2,9899
2,9484
2,9081
2,8551
2,8324
2,751
2,7323
2,6787
2,6424
2,5937

4. Dihydrate B de la revendication 3, dans lequel un spectre d'intensité relative caractéristique est le suivant :

d	I/I_1
9,9045	100,00
6,9985	0,39
6,763	0,17
6,4079	0,13
6,1548	0,85
6,0611	0,99
5,8933	0,35
5,6987	0,12
5,4395	1,30
5,1983	0,67
5,0843	0,24
4,9478	0,34
4,7941	6,53
4,696	1,26
4,5272	2,65
4,4351	2,18
4,3474	1,85
4,2657	0,49

(suite)

d	I/I_1
4,1954	0,69
4,0555	0,42
3,9903	0,89
3,9244	1,52
3,8561	0,99
3,8137	1,44
3,7671	0,92
3,6989	1,78
3,6527	0,60
3,5665	0,34
3,4879	1,41
3,3911	0,27
3,3289	0,20
3,2316	0,31
3,1982	0,19
3,1393	0,35
3,0824	0,18
2,9899	0,26
2,9484	0,38
2,9081	0,29
2,8551	0,37
2,8324	0,49
2,751	0,37
2,7323	0,64
2,6787	0,23
2,6424	0,38
2,5937	0,21

5. Dihydrate de la revendication 4, dans lequel le dihydrate est pur, c'est-à-dire qu'il contient moins de 20% de dihydrate non souhaité.

6. Composé de formule I, dans laquelle le dihydrate est un polymorphe cristallin de dihydrate E d'olanzapine présentant un spectre de diffraction de rayons X réalisé sur la poudre caractéristique comme représenté par les espaces (d) suivants entre les plans comme présenté dans le tableau 3

Tableau 3

d
9,8710
9,5514
6,9575
6,1410
6,0644
5,9896
5,8774
4,7721
4,6673
4,5171
4,4193
4,3540
4,2539

Tableau 3 (suite)

d
4,2369
4,0537
4,0129
3,8555
3,7974
3,6846
3,5541
3,4844
3,4740
3,4637
3,3771
3,1245
2,9403

7. Dihydrate E de la revendication 6, dans lequel un spectre d'intensité relative caractéristique est le suivant :

d	I/I_1
9,9178	100,00
9,6046	16,75
7,0163	2,44
6,1987	8,78
6,0971	10,62
5,9179	1,73
4,8087	50,14
4,714	10,24
4,5335	14,20
4,4531	7,80
4,3648	3,04
4,276	4,50
4,0486	2,76
3,8717	5,09
3,8292	13,39
3,7053	17,24
3,5827	4,82
3,4935	13,22
3,3982	2,01
3,3294	1,30
3,2026	0,98
3,145	2,66
3,1225	1,63
3,088	2,11
2,9614	2,49
2,9014	1,03
2,8695	2,06
2,8359	1,63
2,7647	1,95
2,7582	1,68
2,7496	1,84
2,7421	1,03
2,7347	1,36

(suite)

d	I/I_1
2,6427	2,01

8. Composé de la revendication 7, dans lequel le dihydrate est pur, c'est-à-dire qu'il contient moins de 20% de dihydrate non souhaité.

9. Procédé pour la préparation de la forme II substantiellement pure contenant moins de 0,5% d'impuretés chimiques non souhaitées ou de solvant organique résiduel, comprenant le séchage d'un dihydrate d'olanzapine jusqu'à ce que la forme II souhaitée soit préparée.

10. Procédé de la revendication 9, dans lequel le dihydrate est séché dans un four à vide à 40°C jusqu'à 70°C.

11. Procédé de la revendication 10, dans lequel le dihydrate est le dihydrate D.

12. Procédé de la revendication 10, dans lequel le dihydrate est le dihydrate B.

13. Procédé de la revendication 10, dans lequel le dihydrate est le dihydrate E.